Food for Thought: The Ketogenic Diet and Adverse Effects in Children

Early- and Late-Onset Complications of the Ketogenic Diet for Intractable Epilepsy

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Epilepsia 2004;45:1116–1123

PURPOSE: This study was undertaken to evaluate the exact limitations of the ketogenic diet (KD) and to collect data on the prevention and management of its risks.

METHODS: Patients (129) who were on the KD from July 1995 to October 2001 at our epilepsy center were assessed in the study. Early-onset (within 4 weeks of the commencement of the KD until stabilization) and late-onset complications (occurring after 4 weeks) were reviewed.

RESULTS: The most common early-onset complication was dehydration, especially in patients who started the KD with initial fasting. Gastrointestinal disturbances, such as nausea/vomiting, diarrhea, and constipation, also were frequently noted, sometimes associated with gastritis and fat intolerance. Other early-onset complications, in order of frequency, were hypertriglyceridemia, transient hyperuricemia, hypercholesterolemia, various infectious diseases, symptomatic hypoglycemia, hypoproteinemia, hypomagnesemia, repetitive hyponatremia, low concentrations of high-density lipoprotein, lipoid pneumonia due to aspiration, hepatitis, acute pancreatitis, and persistent metabolic acidosis. Late-onset complications also included osteopenia, renal stones, cardiomyopathy, secondary hypocarnitinemia, and iron-deficiency anemia. Most early- and late-onset complications were transient and successfully managed by careful follow-up and conservative strategies. However, 22 (17.1%) patients ceased the KD because of various kinds of serious complications, and 4 (3.1%) patients died during the KD, two of sepsis, one of cardiomyopathy, and one of lipoid pneumonia.

CONCLUSIONS: Most complications of the KD are transient and can be managed easily with various conservative treatments. However, life-threatening complications should be monitored closely during follow-up.

COMMENTARY

Options for treating children with pharmacoresistant epilepsy are limited. In the face of medication failure, families are often overwhelmed, while treating physicians are frustrated at the prospects of dealing with chronic, unremitting seizures. For many children, excisional surgery is not a viable option or is held out as a treatment of last resort.

Enter the ketogenic diet. The diet has been used successfully to treat patients with epilepsy since the early years of the last century (1,2). The benefits of establishing a ketotic internal milieu are by now indisputable, with numerous studies establishing its efficacy in a high proportion of patients with intractable epilepsy (3–5). Remarkably, the induction of ketosis eliminates or reduces both generalized and partial intractable seizures to a degree unmatched by even the newer antiepileptic drugs. The diet also holds promise for adolescents and adults (6,7). Public awareness of the ketogenic diet has risen to new heights through lay-oriented publications and educational pamphlets, Web-based information, and a recent made-for-television movie, starring Meryl Streep as the parent of a child whose seizures were miraculously eliminated through dietary management. The movie was made by Jim Abrahams, an established producer and the child's parent (8).

Public acclaim and medical advocacy for the ketogenic diet reflect its long track record of efficacy. Why, one might logically ask, should the ketogenic diet not become the primary therapeutic option when the diagnosis of epilepsy is first established? After all, dietary manipulation largely eliminates the need for drugs, with all of their potential side effects, and surgery, with its attendant risks, including possible brain damage and death. No simple answers to this question exist, but several points seem clear. It is now recognized that the ketogenic diet is not suitable for every child with epilepsy. As a consequence of the restricted dietary choices and considerable time and energy needed to maintain ketosis, the diet is not "user friendly." Children often refuse the diet as a personal choice, and diet-induced social modifications are family stressors. The negative social consequences of severe dietary restrictions may render it difficult to implement ketosis or impossible to maintain. In many countries, local food sources are not appropriate for properly implementing the ketogenic diet. Even in developed countries, the

ketogenic diet is typically offered only at specialized centers for epilepsy with a team of consultants capable of working with families and children on dietary therapy.

The medical consequences of the ketogenic diet are another formidable but less well documented hurdle. Although underdocumentation is not altogether unusual in the case of newer therapies, the paucity of large-scale, long-term adverse-effect data for a well-established treatment regimen is disconcerting. Clinical studies and reviews of the ketogenic diet more often report quantitative measurements of efficacy, whereas relatively less information is available regarding medical complications. Exceptions exist: Balaban-Gil et al. reported a 10% rate of serious complication in 52 children with refractory epilepsy (9), and anecdotal reports of coma and death are often attributed to unmasked metabolic disorders (10,11). Although most clinicians are cognizant of the risks associated with the diet, an information gap remains regarding the prevalence of serious medical complications.

In a recently published study that focuses on tolerability and complications of the ketogenic diet, Kang and coworkers prospectively followed up a cohort of 129 children treated with the ketogenic diet for a mean duration of 1 year. Seizure diagnoses, antiepileptic drug regimens, and efficacy data were similar to those of other children on the diet, suggesting that the study population was reasonably representative of patient populations at other tertiary referral centers for pediatric epilepsy. Eighty-seven patients had ketosis induced, according to the Johns Hopkins protocol. Scheduled patient and laboratory assessments were similar to those in use in most clinical centers. The investigators classified complications as either early or late onset, depending on whether they were reported within 4 weeks of introducing the ketogenic diet until stabilization, or thereafter. The occurrence of an abnormality triggered more frequent surveillance.

Within the first 4 weeks, dehydration and gastrointestinal complications were the most commonly encountered complications. Infectious diseases, aspiration pneumonia, serum lipid abnormalities, hyperuricemia, hypoglycemia, electrolyte imbalance and acidosis, hepatitis, and acute pancreatitis also occurred. After the first 4 weeks, study patients were still prone to almost all of the early complications except dehydration, pancreatitis, and hyponatremia. In nearly 15% of the patients, osteopenia, renal stones, hydronephrosis, iron deficiency anemia, secondary hypocarnitinemia, and cardiomyopathy developed after the first month of ketosis. Fortunately, most early- and late-onset complications improved with conservative management and did not cause the patient to exit the diet. However, 22 patients dropped out as a result of a variety of adverse effects, including gastrointestinal disturbance, infections, aspiration pneumonia, pancreatitis, electrolyte disturbance, and osteopenia. No significant differences were found in the rate of complication for patients who were taking or not taking valproate. Four (3.8%) patients died during the study period. One child with pyruvate dehydrogenase deficiency died of cardiomyopathy. One patient died of lipoid pneumonia after aspirating, and in two patients, serious infectious diseases developed. The latter three died within 60 days of initiating the diet; all had significant underlying brain damage.

The frequent complications and poor tolerability of the ketogenic diet reported by Kang and colleagues are not altogether surprising, and similar complications have been described previously (9,12,13). It is known, for example, that tolerability of the ketogenic diet is the single most important factor limiting individual acceptance, and the incidence of complications typically restricts implementation of the diet to tertiary pediatric epilepsy centers. Although most complications respond to conservative management, the availability of an experienced multidisciplinary team facilitates both early detection of complications and prompt therapeutic manipulation. The study by Kang et al. confirms that tolerability and complication-related issues are the rule, not the exception, and that medical surveillance must be maintained throughout the entire period of dietary treatment. As the study demonstrates, complications occur even after a significant period has elapsed. Late-developing complications also accompany pharmacologic treatment, but the majority appear within 6 months of introducing the drug. The authors do not specify the overall incidence of complications, but their data suggest that it is probably quite high.

The mortality rate reported by Kang et al. also is high and decidedly above the mortality experience encountered at other centers, superseding mortality rates for antiepileptic drugs and surgery. Although death of patients on the ketogenic diet is reported at other centers (11), the mortality reported in the present study is unusual. It should be remembered, however, that patients referred for the ketogenic diet often have severe underlying encephalopathy, which places them at substantial risk for complications (13). Furthermore, neurometabolic disorders are a recognized cause of pharmacoresistant epilepsy that may be undiagnosed, even at sophisticated centers. Instituting ketosis will unmask symptoms that would otherwise remain silent.

The dropout rate from complications in the Kang et al. study was more than twice the dropout rate from complications at other centers (11,13). The reasons for this discrepancy are unclear and should raise questions about the uniformity of the ketogenic diet worldwide. Possible explanations include intrinsic population differences, different surveillance practices, or varied social and cultural factors. One wonders, for example, whether the Kang et al. study patient who died of complications of cardiomyopathy could have been identified before starting the diet. Furthermore, certain complications documented at other centers, such as bruising (14), were notably absent among

the Kang et al. study patients. Differences in morbidity, mortality, and types of complications reported by Kang et al. are disturbing and may not be generalizable to patients in other parts of the world.

What are the lessons to be gained from the study of Kang et al.? The authors state that most of the complications of the ketogenic diet are transient and can be managed with conservative treatment. They also point out that life-threatening complications should be monitored closely. Both statements are true, but healthcare providers of children with pharmacoresistant epilepsy who are involved with the ketogenic diet would do well to observe caution and tread carefully. Simply put, the ketogenic diet is complicated, but for a small group of children, its complications are severe and life threatening. The scope of medical complications and their potential seriousness mandate a high level of expertise, practical experience, and a high index of suspicion. Establishing accurate rates of tolerability and complications may be possible only through large multicenter trials.

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